Allergy Abstracts

Editor

MURRAY M. ALBERT
Brooklyn, N. Y.

Editorial Board

KATHERINE BOWMAN
Brooklyn, N. Y.

HAROLD J. FRIEDMAN
Cleveland, Ohio

BERNARD B. SIEGEL
Far Rockaway, N. Y.

MAX GROLNICK (EX OFFICIO)
Brooklyn, N. Y.

Associate Editors

MONROE COLEMAN
Stamford, Conn.

EUGENE H. WALZER
Bridgeport, Conn.

ELOISE KAILIN
Washington, D. C.

ISRAEL GLAZER
Tel Aviv, Israel

RICHARD D. WISEMAN
Syracuse, N. Y.

JOSE LUIS CORTES
Mexico, D. F.

JEROME SHERMAN
Baltimore, Md.

Advisory Editor

MATTHEW WALZER
Brooklyn, N. Y.

From the Allergy Division of
The Jewish Hospital of Brooklyn

Volume 22, Number 1 January, 1957

Asthma and Hay Fever

Five Years' Experience With Hormone Therapy of Asthma in Private Practice.

Walton, C. H. A.: Canad. M. A. J. **75**: 557, 1956.

The author reviewed his experiences with hormones in the treatment of 153 asthmatics over a 5-year period. They constituted about 10 per cent of the asthmatic patients under his observation during this time. Of these 153 patients, 87 were females and 66 were males. Ten were under 15 years of age, 63 were between the ages of 16 and 45, while 80 were over 46. About 10 per cent of the patients had a strictly seasonal problem, while almost one-half of the cases were complicated by an allergic rhinitis. About 60 per cent had recurrent infections and 15 per cent were sensitive to aspirin.

Four patients had inactive tuberculosis before starting on hormone therapy. In one there was a reactivation, but it was necessary to continue hormone therapy because of severe asthma. The patient did well on sanatorium care plus antituberculous chemotherapy. Of 3 patients with peptic ulcers, one required a subtotal gastrectomy and another developed a severe hemorrhage but

recovered uneventfully. Of 28 hypertensives under treatment, the blood pressure remained essentially unchanged in 25. Two of the patients succumbed to cerebral complications and one developed congestive heart failure.

Nine pregnant women who were treated delivered normal babies uneventfully, but one woman stopped her medication against advice and died 4 weeks post partum. Eighteen of the patients required major surgery. Each patient was given 100 mg. or more of cortisone intramuscularly just prior to and immediately after surgery. One patient died of asphyxia from aspiration of blood following radical surgery of an antrum but all others recovered uneventfully.

Clinical emphysema usually improved or disappeared and nasal polypi shrunk and frequently did not reappear while patients were under treatment.

Because of the ease of administration, most patients received cortisone rather than ACTH. About one-half of the patients had complete relief of symptoms while on steroids and the others required supplemental medications. The average maintenance dose of cortisone was between 50 and 75 mg. daily, but many patients required 100 mg. or more daily to obtain good relief.

The usual side effects of moon facies, edema of the lower extremities, hirsutism, and nervous symptoms were encountered but only occasionally necessitated withdrawal of therapy. Obesity was common and troublesome. Although 15 of the patients died while under treatment, the author is of the opinion that about one-half of them might have been saved by more adequate hormone therapy, and that a few of the patients probably died of masked infections. R. W.

Treatment of Spontaneous Pneumothorax. Lefemine, A. A., O'Hara, E. T., and Lynch, J. P.: J. A. M. A. **162**: 622, 1956.

In a series of 42 nontuberculous patients with simple pneumothorax three different methods of treatment were tried. No underlying pulmonary disease was found in 32 of the cases; in 10, the etiology included emphysema, asthma, bronchiectasis, bronchitis, and sarcoma. In 15 of the cases, with partial collapse of the affected lung, rest was sufficient treatment and the average time required for complete re-expansion of the lung was 12 days. Closed thoracotomy was tried in 12 of the more severe cases. This consisted of the insertion into the second intercostal space anteriorly of a #16 soft rubber catheter which was connected to a two-bottle suction system maintained at 10 cm. H_2O. This procedure required from 1 to 9 days, or an average of three and one-half days, for complete expansion of the lung. Hemothorax and empyema developed as a complication of this therapy in one patient. The technique of repeated aspirations required an average of 15 days for the full re-expansion of the lungs. Although rest was the safest treatment in terms of infection, it was noted that it carried with it the danger of chronic pneumothorax. It was concluded that, as a method of treatment, repeated aspirations held no advantage over a carefully performed closed thoracotomy. M. C.

Dermatology

Some Aspects of Occupational Dermatoses. Klauder, J. V.: J. A. M. A. **160**: 442, 1956.

Of 5,483 cases of cutaneous diseases examined by the author as claimants of workmen's compensation, 2,407 (43 per cent) were regarded as occupational in origin. Of the latter, 27.7 per cent were cases due to primary irritants, 22.1 per cent were due to trauma, 15.2 per cent were due to sensitizing substances, 15.0 per cent were due to wet work (water alone, soap and water,

and alkaline salt detergents), 9.9 per cent were due to cleansing agents, 7.6 per cent were due to petroleum products and other causes of folliculitis, and 2.3 per cent were due to physical and biologic agents. In the diagnosis of these conditions, it was stressed that patch testing was indicated only in cases of allergic (sensitization) dermatitis. In the author's experience, patch tests were of limited value in the diagnosis of occupational dermatoses. Workers with allergic dermatitis were ordered to change their work or, in selected cases, to continue the same work, employing protective measures. In the entire group of occupational dermatoses, there were no patients who developed total permanent disability or involvement of the entire skin. M. C.

Allergic Hypersensitivity to an Antiseptic Soap. Blank, I. H.: J. A. M. A. **160**: 1225, 1956.

A soap (Lifebuoy) containing tetramethylthiuram disulfide, an antiseptic, was studied for its possible sensitizing properties. This chemical is also used as an accelerator in the rubber industry. Five patients known to be sensitive to this chemical in rubber adhesives were used as subjects. Patch tests with various materials were done on these subjects. All subjects who showed a vesicular reaction to the rubber accelerator also showed a similar reaction to the antiseptic soap and to an 8 per cent solution of this soap. No significant reactions were obtained with a control soap which did not contain the antiseptic. A sixth subject who was allergic to a chemically related rubber accelerator failed to react to either the antiseptic or to the soap containing the antiseptic. Although few cases of sensitization to this antiseptic soap have been reported, its ability to produce a dermatitis must be considered.

M. C.

Sensitization to Facial Tissues With Urea-Formaldehyde Resin (Wet-Strength). Peck, S. M., and Palitz, L. I.: J. A. M. A. **160**: 1226, 1956.

Two types of facial tissues were studied for their sensitization capability. Tissue "B" contained a urea-formaldehyde resin which was added to give wet-strength to the material. Tissue "A" did not contain either melamine-formaldehyde or urea-formaldehyde resin. A repeated insult patch test technique was used in 50 normal subjects. Patch tests were applied to the outer area of the upper arm of each subject for 24 hours and then removed. The skin was allowed to recuperate for 24 hours and the cycle of contact and recuperation was repeated 15 times. Alternate arms were used for each tissue. Simultaneously, each tissue was rubbed 90 times per minute on one or the other cheek of each subject. This usage test was continued for a 30-day period. In 2 cases, positive patch and usage tests developed with tissue "B." A third case developed a positive patch test to tissue "B." No reactions resulted from tissue "A." These results were considered proof of the sensitizing capacity of facial tissues impregnated with synthetic resins such as urea-formaldehyde. It is important that a patch test be done in suspicious cases with a 1 per cent solution of formaldehyde, as well as with the suspected tissue, since the amount of free resin or formaldehyde available in the latter is small and may not elicit a positive reaction. M. C.

Hydroxyzine (Atarax) Hydrochloride in Dermatological Therapy. Robinson, H. M., Jr., Robinson, R. C. V., and Strahan, J. F.: J. A. M. A. **161**: 604, 1956.

A group of patients with various dermatoses which are generally regarded as being influenced by psychogenic factors were treated with hydroxyzine hydrochloride, a tranquilizing drug. The effects of the drug were evaluated

by administering alternate courses of the drug and a placebo and observing the effect on the skin lesions. Among 41 patients suffering from general atopic dermatitis, localized neurodermatitis, pruritus ani, or factitious dermatitis, 36 showed clinical improvement while taking the drug. Recrudescence occurred with the placebo. Of 12 patients with atopic dermatitis, 11 demonstrated noticeable improvement with hydroxyzine. Side effects of the drug were infrequent and mild; no toxic reactions were observed. M. C.

Allergic Eczematous Contact Dermatitis Due to Metallic Nickel. Fisher, A. A., and Shapiro, A.: J. A. M. A. **161**: 717, 1956.

In a large dermatology clinic, 198 cases of nickel dermatitis were observed over a 5-year period. There were 180 women and 18 men in this group. The most common locations of dermatitis were on the ear lobes, thighs, and wrists. Earrings, garter clasps, and metal chairs were the most common sources of nickel contact. Most patients were quite successful in avoiding contact with nickel objects, once they were made aware of the cause of the dermatitis. Forty patients who had been patch tested with nickel 2 to 17 years previously were again patch tested with 5 per cent nickel sulfate. Positive reactions occurred in 36 of these patients. No cross reactions to potassium dichromate or copper sulfate were observed. Nickel coins were considered to be an infrequent cause of nickel dermatitis. M. C.

A Comparison of the Inhibitory Effect of 9α Fluor-Hydrocortisone Acetate and Hydrocortisone Acetate Ointments on Eczematous Reactions Produced by Electrophoresis. Haxthausen, H.: J. Invest. Dermat. **26**: 111, 1956.

In 8 patients with known contact sensitivity to such substances as mercury, nickel, and chromate, the specific antigen was introduced into the skin of the back by means of electrophoresis. Immediately thereafter, the electrophoretic-treated areas were patch tested with 2.5 per cent concentrations of 9α fluor-hydrocortisone acetate and hydrocortisone acetate ointments. In 2 additional cases, the antigen was applied directly to the skin in alcoholic solution and the patch tests were performed after the alcohol had evaporated. Reactions read after 24 and 48 hours indicated a superiority of the fluor-compound with regard to the inhibitory effect on the eczematous lesion. However, the effect was neither constant nor complete. The greater suppressive action of the fluor-compound was attributed partly to its better skin penetration capacity. M. C.

A Clinical Evaluation of Prednisone in the Treatment of Dermatoses. Rein, C. R., and Bodian, E. L.: Arch. Dermat. **73**: 378, 1956.

The authors discuss the value of prednisone in the treatment of 41 patients between the ages of 8 and 75 years suffering from various dermatoses. Many of these individuals had previously received cortisone or hydrocortisone, but their therapy had to be interrupted due to severe side reactions. All the patients were given Meticorten orally in order to learn whether or not the same type of side reactions would recur. About 50 per cent of the patients suffered from allergic dermatoses, most of which were diagnosed as atopic dermatitis or urticaria. Meticorten therapy was started only after all previous therapy had been discontinued for at least 2 weeks or when a marked

exacerbation of the eruption had taken place. The diet was not restricted and doses as high as 60 mg. daily were given when necessary to obtain relief.

About 75 per cent of the patients obtained dramatic relief. A few patients did not improve, even though they received up to 60 mg. of Meticorten daily. The initial clinical response was slower with prednisone than with hydrocortisone. Interestingly enough, the only important side reaction was moon facies. This complication was observed in 2 patients who had had a similar reaction from cortisone or hydrocortisone, and it also occurred in 3 other patients who had not previously received steroid therapy. Several other mild side effects were noted, but they rarely necessitated interruption of the treatment. These included increased appetite with weight gain, gastric distress, menstrual disturbance, acne, hot flushes, increased sweating, headaches, vertigo, weakness, depression, and insomnia. In an addendum to this paper, the authors state that they have treated an additional 171 patients with prednisone with similar results. R. W.

Stimulation of the Cell-Linked Defence Forces of the Skin. Mechanism of Action of Certain Topical Agents. Kátó, L., and Gözsy, B.: Canad. M. A. J. **73**: 31, 1955.

A suspension of barium sulfide was used to depilate the abdomens of white mice of both sexes. The next day, those animals showing skin lesions in the depilated area were discarded. All solutions or ointments to be tested were gently rubbed into the skin with a cotton swab for two minutes. Each agent being tested was dissolved or suspended in white petrolatum and in Transdermine (triethanolamine.) Immediately after the skin was rubbed, 0.5 ml. of an India ink suspension was injected into the tail vein. The substances were tested in each of the two vehicles on 32 different animals. The following materials were studied: histamine, coal tar, chrysarobin, resorcin, ichthyol, camphor, menthol, thymol, pyrogallic acid, salicylic acid, sodium salicylate, benzoic acid, boric acid, sodium tetraborate, tannic acid, tannalbin, bismuth subnitrate, bismuth subsalicylate, zinc oxide, titanium oxide, titanium peroxide, titanium tannate, and titanium salicylate.

The sites were observed at 1, 2, and 24 hours following the injection of the dye. Phagocytosis, when it developed, was usually evident within 1 hour and was manifested by the appearance of a black stain at the site of application of the active substance. Microscopic examination of the black-stained tissues always revealed India ink particles in the endothelial cells of the skin capillaries. An intensive phagocytic effect was obtained with histamine and coal tar. Transdermine was twice as effective as a carrier for coal tar as white petrolatum. Chrysarobin, ichthyol, and resorcin induced marked phagocytic activity but were irritating to the skin. Pyrogallic acid caused a necrosis of the skin, while benzoic, boric, and tannic acids, as well as sodium salicylate, menthol, sodium tetraborate, and tannic albuminate were without effect. Camphor, thymol, and salicylic acid were weakly effective, but the salicylic acid was somewhat irritating. Zinc oxide and titanium oxide were inactive, while bismuth subnitrate and bismuth subsalicylate showed mild activity. Titanium tannate and salicylate induced intense phagocytosis, especially when Transdermine was the carrier. The authors suggest that good therapeutic results may be expected in eczematous dermatoses when the drug employed is capable of stimulating the cell-linked defence mechanism to increased activity. This response was measured by evaluating the amount of phagocytosis which occurred in the endothelial cells of the skin capillaries following topical application of the therapeutic agents. R. W.

Clinical Evaluation of Topical Fludrocortisone. Van de Erve, J., Jr.: Arch. Dermat. **74**: 92, 1956.

The author studied 335 patients with many types of dermatitis in order to compare the effectiveness of local hydrocortisone and fludrocortisone (9α-fluorohydrocortisone) therapy. Both materials were applied as ointments and lotions, the fludrocortisone in 0.1 per cent, 0.25 per cent, and 0.5 per cent concentrations and the hydrocortisone in 1 per cent and 2.5 per cent concentrations. The steroid preparations were paired, the fludrocortisone being one-tenth as strong as the hydrocortisone. The patients were told to apply the lotion or ointment three times daily to the affected areas. Some patients were asked to alternate preparations, but in most cases simultaneous contralateral applications were prescribed. Most patients were treated for from 14 to 21 days.

About one-half of the patients were given a placebo preparation containing only the vehicle. About 3 per cent reported improvement from the placebo. When the placebo vehicle and the steroids were used in paired comparison, patients invariably reported that the vehicle was less helpful than the drug-containing preparation. Fludrocortisone was equally as effective as hydrocortisone in a concentration one-tenth as strong. If the concentration of either preparation was doubled, the patients quickly noted greater relief. A few patients complained of a burning sensation when the steroids were applied, but patch tests in these patients gave negative reactions. If the patients had acute weeping lesions, their tolerance for these preparations was limited and at times the medication appeared to aggravate the condition. Patients with chronic dry scaling or lichenified dermatoses obtained the best results from the topical corticoid therapy. Patients with atopic dermatitis or contact eczematoid dermatitis preferred the lotion form, especially during the acute phase. If the skin lesion was infected, neither steroid preparation was effective until other medications had been used to clear up the infection. The author suggests that the additional relief obtained from the stronger hormone concentrations does not justify the greater cost of the stronger preparations.

R. W.

Miscellaneous Allergies

Thrombocytopenic Purpura Due to Quinidine. II. Serologic Mechanisms. Bolton, F. G.: Blood **11**: 547, 1956.

The results of serologic tests made on the blood of a patient suffering from thrombocytopenic purpura due to quinidine are reported in detail. An abnormal fraction which caused agglutination and lysis of the patient's platelets or the platelets from normal individuals in the presence of quinidine was found in the plasma or serum. If quinine was substituted for quinidine, this reaction did not take place. Complement fixation tests showed that complement was fixed when normal platelets, quinidine, and the patient's serum were incubated with complement. If any one of the three factors was omitted, fixation of complement did not occur. Normal platelets could absorb the serum or plasma factor only in the presence of quinidine. When the platelets had absorbed this factor, they could fix complement.

When normal platelets were treated with quinidine and washed with saline, they were not able to fix complement in the presence of the patient's serum until more quinidine had been added. Quinidine could also be readily dialyzed out from the patient's plasma-quinidine mixture. There was no firm bondage between these three factors. This was further demonstrated by the fact that when platelets previously treated with serum and quinidine were dialyzed against saline, the complex dissociated into the three constituents

(platelet, quinidine, and plasma). By electrophoretic methods, the essential serum fraction was shown to be in the gamma-globulin fraction. This finding was substantiated by ammonium sulfate fractionation. Heating at 65 to 70° C. for 30 minutes destroyed the complement-fixing capacity of the serum. Concentrations of 0.3 mg. per liter of quinidine caused platelet agglutination in vitro. This concentration is surpassed in normal persons receiving 0.6 Gm. of quinidine by mouth.

Prausnitz-Küstner studies performed to demonstrate a possible antigenic relationship between platelets and blood vessel endothelium gave negative results.

In conclusion, the author states that serologic testing failed to demonstrate any union between normal platelets and quinidine or between the patient's plasma and quinidine. The mechanism by which quinidine presumably confers antigenicity upon platelets is still unknown. R. W.

Repeated Anaphylactic Reactions in a Patient Highly Sensitized to Penicillin. A Case Report. Bierlein, K. J.: Ann. Allergy **14**: 35, 1956.

A nurse employed in a physician's office complained of nasal and ocular symptoms during working hours. These symptoms were exaggerated whenever she removed syringes from the sterilizer. She had had several mild to severe systemic reactions to oral and injected penicillin and to ACTH and cortisone. An intracutaneous skin test dose of 0.000003 unit of penicillin was followed within two minutes by a severe constitutional reaction. An extract was made of dust gathered from her place of employment. Positive reactions were obtained with the extract by passive transfer and by direct skin tests in a 1:625 dilution. The patient was then given a subcutaneous dose of 0.1 c.c. of this dilution to which Chlor-Trimeton had been added. Within two minutes she began to exhibit signs of a severe constitutional reaction which was controlled by heroic treatment. Investigation revealed that the vial from which the Chlor-Trimeton had been withdrawn had very likely been punctured previously by a syringe containing penicillin. Passive transfer sites prepared with the patient's serum gave positive reactions when tested with Chlor-Trimeton solution from this vial. The patient had previously had a severe shock reaction to an injection of 40 units of ACTH. A positive passive transfer reaction was obtained when sites sensitized with the patient's serum were tested with 0.01 units of aqueous ACTH of the same brand with which she had been treated. In further passive transfer studies, a 1:25 dilution of Salk antipolio vaccine gave a positive reaction. This would indicate that extremely small doses of penicillin may produce severe reactions and even the minute amount of the antibiotic contained in the Salk vaccine may prove dangerous to a sensitive individual. H. F.

Agranulocytosis Associated With Chlorpromazine Therapy. Horbaczewski, J.: Canad. M. A. J. **75**: 412, 1956.

Two patients who received chlorpromazine therapy developed fatal agranulocytic reactions. They were members of a large series of cases in a mental institution who were being treated with chlorpromazine in order to evaluate the effectiveness of the drug. The medication had been given for about two months before the agranulocytosis developed. One patient received 50 mg. three times daily for a maintenance dose; the other patient was started on 25 mg. three times daily and was gradually raised to 300 mg. three times daily

before the dose was tapered down to 25 mg. three times daily. After the onset of the reaction, each patient ran a rapid downhill course. Neither patient received steroid therapy but the author suggests that if one postulates an immunologic mechanism in this condition such therapy might be beneficial.

The author reviewed the literature and noted nine previously reported cases of agranulocytosis caused by chlorpromazine. To date no one has reported the finding of granulocytic agglutinins in the blood of these patients. The fact that a certain length of time has to elapse between the initiation of chlorpromazine therapy and the onset of agranulocytosis, as well as the observation that dosage does not seem to be a determining factor in these cases, tends to support the possibility that an immunologic mechanism may mediate the agranulocytosis. The author estimated the incidence of agranulocytosis in his patients receiving chlorpromazine therapy as 1 in 500. R. W.

Diphenylhydantoin Sensitivity. Report of Fatal Case With Hepatitis and Exfoliative Dermatitis. Gropper, A. L.: New England J. Med. **254**: 523, 1956.

Dilantin (diphenylhydantoin sodium) hypersensitivity, manifested by hepatitis and exfoliative dermatitis terminating in death, was reported in a 29-year-old epileptic Negro. This drug was administered in 0.1 Gm. doses three times daily for six weeks, at the end of which time the patient complained of a "pimply" rash on the forearms and a sore throat. He was put on penicilliln in 300,000 unit doses and on Gantrisin, 4 Gm. daily. The rash became generalized and exfoliative and a generalized lymphadenopathy and jaundice developed. Physical examination revealed an acutely ill man with icteric scleras, a generalized desquamating eruption, a diffuse erythematous flush, and an enlarged liver three fingerbreadths below the right costal margin. The white blood count was 19,000 with 35 per cent eosinophils and 15 per cent abnormal lymphocytes. The urine contained albumin and bile. Because a mistaken diagnosis of infectious mononucleosis was entertained, the Dilantin was continued for three days and then cortisone, transfusions, vitamin K, chlortetracycline, and potassium parenterally were given. Despite these measures, the patient developed generalized bleeding tendencies and died. At autopsy there was a grossly enlarged liver with severe hepatitis which, on microscopic section, showed complete disruption of the lobular architecture. The lining Kupffer cells contained bile pigment, and bile plugs were seen filling many of the canaliculi and small bile ducts. There were also acute necrotizing hemorrhagic bronchopneumonia, mild acute hemorrhagic pancreatitis, and cholemic nephrosis. There were no findings suggestive of periarteritis nodosa. E. W.

Effect of Penicillinase on Circulating Penicillin. Becker, R. M.: New England J. Med. **254**: 952, 1956.

Penicillinase, an enzyme formed by certain bacteria that hydrolyzes and inactivates penicillin, was administered to guinea pigs in 40,000 to 200,000 unit doses. No circulating penicillin could be detected after an hour for a period of 76 hours, although injections of 500,000 to 800,000 units of penicillin were given every 24 to 48 hours for a total dosage of 2 million units. The inactivating action of penicillinase in vivo was found to be the same against both aqueous crystalline penicillin and procaine penicillin. To 20 normal human subjects, injections of 800,000 units of fortified procaine penicillin were given twice daily intramuscularly. After consistent blood levels were established for several days, a single injection of 100,000 to 800,000 units of purified

penicillinase was given intramuscularly to each patient. Within an hour, and for periods up to seven days, no circulating penicillin could be detected despite the fact that the injections of penicillin were continued twice daily.

Intradermal skin testing with aqueous crystalline penicillin in a penicillin-sensitive person produced a 4-plus erythematous wheal reaction. When penicillinase was mixed with penicillin before injection, there was no reaction. When two patients were given three intramuscular injections of 800,000 units of purified penicillinase eight days apart, no localized or generalized sensitivity reactions to the penicillinase were noted. A follow-up study of the use of purified penicillinase in penicillin-sensitive patients is being undertaken. E. W.

Pathogenesis of Eosinophilic Pneumonitis (Löffler's Syndrome). Epstein, W. L., and Kligman, A. M.: J. A. M. A. **162**: 95, 1956.

Eosinophilic pneumonitis developed in 7 of more than 1,000 patients who were receiving hyposensitization injections of 3-pentadecylcatechol, a synthetic chemical that is one of the allergens in poison ivy. The pulmonary symptoms developed suddenly between 8 and 48 hours after the last injection. Sharp chest pains, the production of sputum, and occasional râles were among the common findings. Eosinophilia, leukocytosis, and variable degrees of patchy pneumonitis occurred consistently. It was postulated that the pulmonary infiltrates were caused by the trapping of eosinophils in the lung and not, as commonly believed, by an allergic pulmonary reaction. M. C.

Anaphylaxis

A Study of the Mechanism of the Schultz-Dale Reaction. Geiger, W. B., Hill, E. M., and Thompson, M.: Proc. Soc. Exper. Biol. & Med. **92**: 793, 1956.

Theories for the mechanism of the Schultz-Dale reaction fall into two overlapping groups: (1) liberation of a stimulant such as histamine or acetylcholine as a result of an antigen-antibody reaction and (2) involvement of a nerve mechanism.

It was found that inhibitors that block respiration (cyanide), other oxydative processes (fluoracetate), and glycolysis (fluoride) did not seriously affect the ability of antigen to cause contraction of sensitized smooth muscle. The same substances, under similar conditions, did not alter contraction induced by acetylcholine or histamine. Further experiments were tried to determine whether substances known to block transmission in nerves were capable of blocking the Schultz-Dale reaction. It was found that anesthetics, such as Nupercaine and urethane and certain chemicals such as alcohol derivatives did not affect the contraction due to histamine or acetylcholine, although they nonspecifically blocked transmission of impulses in different nerves.

The nervous structure involved in contraction of the guinea pig ileum includes preganglionic fibers that enter ganglia of Auerbach's plexus from which postganglionic fibers lead to nerve endings associated with the smooth muscle. The Schultz-Dale reaction remained unchanged in the presence of agents, such as hexamethonium bromide and benzoquinonium, that block at the ganglia. On the other hand, botulinum toxin type D which has a very specific paralyzing action upon the postganglionic fibers blocked the Schultz-Dale reaction induced by antigen but not that induced by acetylcholine. The histamine reaction was suppressed to a variable degree when this same toxin was used.

The results of these studies seem to indicate that the most likely mechanism for the Schultz-Dale reaction involves stimulation of postganglionic nerve fibers by antigen in the presence of antibodies resulting in muscle contraction. S. Stousland.

Pulmonary Vascular Changes in the Mouse During Anaphylactic Shock. Kind, L. S., and Gallemore, J. I.: Proc. Soc. Exper. Biol. & Med. **92**: 345, 1956.

Female mice were sensitized intraperitoneally with either *Hemophilus pertussis* vaccine and horse serum or with the pertussis vaccine alone. Challenge doses of horse serum were administered intravenously 10 to 20 days later. Prior to the challenge injection, the animals were anesthetized with pentobarbital sodium and a tracheotomy was performed. A needle inserted in the tracheal lumen permitted oxygen administration and normal gaseous return from the lungs. A thoracotomy was then performed and the lung was exposed. The edge of the lung was transilluminated by the quartz rod method and microscopic observations and motion pictures were made through a Leitz binocular stereoscopic microscope with a special camera attachment.

Seventy per cent of the 53 sensitized mice showed at least one of three pulmonary vascular phenomena after the challenge dose of horse serum: clumping of red cells (sludge); arteriolar constriction; and embolization. Embolization occurred in 51 per cent of the reacting mice. The mice sensitized with pertussis vaccine only failed to show any of these changes after challenge doses of horse serum.

The above phenomena appeared in the sensitized mice within a few minutes after the challenge dose was given and disappeared after a few minutes. Most of the sensitized animals survived the challenge injection of horse serum. This is in contrast to the 80 to 100 per cent fatality to similar challenge doses in similarly sensitized mice which were not subjected to anesthesia, exposure of the lung, and oxygen insufflation. It appeared likely that these procedures had a protective effect in mouse anaphylaxis. The significance of the pulmonary vascular changes seen in mice during anaphylactic shock is that they are very similar to those previously observed in rabbits and guinea pigs in anaphylaxis. The vasoconstriction, embolization, and sludge may be responsible for the cyanosis and respiratory embarrassment observed in the intact mouse during shock. The nature of the emboli is unknown but they are thought to be clumps of leucocytes sticking to an antigen-antibody precipitate. B. S.

Effects of Heat on the Sensitizing and Shocking Properties of Hemophilus Pertussis. Kind, L. S.: J. Immunol. **77**: 115, 1956.

Mice were inoculated intraperitoneally with unheated pertussis vaccine or with vaccine heated at 80° C. for 30 minutes. Five days later the animals were challenged intraperitoneally with various doses of histamine dihydrochloride. The LD_{50} of histamine in the mice inoculated with the heated vaccine was 36 mg. per kilogram as compared with 3.5 mg. per kilogram in mice injected with untreated vaccine. Thus, heating at 80° C. for 30 minutes reduces the histamine-sensitizing property of *Hemophilus pertussis*. However, mice treated with heated vaccine were far more sensitive to histamine than uninoculated mice in which the LD_{50} was greater than 1,000 mg. per kilogram. All mice that were sensitized with heated pertussis vaccine and challenged with unheated vaccine survived. Of the mice sensitized with unheated vaccine and challenged with unheated vaccine, only 58 per cent survived. Hence, heating the

vaccine to 80° C. for 30 minutes destroys its ability to sensitize mice to unheated vaccine. Mice sensitized with unheated vaccine and challenged with heated vaccine showed a 38 per cent survival rate. Thus, heating vaccine does not deprive it of its power to kill mice previously sensitized with untreated vaccine.

Seventy-eight per cent of mice sensitized with heated vaccine plus horse serum survived challenge doses of horse serum. This result was similar to that found in the group of mice sensitized with horse serum alone. In contrast, only 29 per cent of the mice inoculated with unheated vaccine and horse serum survived challenge doses of horse serum. Hence, heated vaccine is incapable of sensitizing mice to anaphylactic shock.

In other studies, heating the pertussis vaccine at 60° C. for one hour had no effect on its histamine-sensitizing, pertussis-sensitizing, or anaphylaxis-sensitizing properties. The results of studies with pertussis vaccine heated at 100° C. for one hour were similar to those obtained with vaccine heated at 80° C. for 30 minutes. The fact that heated pertussis vaccine could kill previously sensitized mice yet could no longer sensitize suggested that the shocking and sensitizing components of *Hemophilus pertussis* were different substances. The author suggests that the shocking component may be an endotoxin or endotoxin-like substance and that the sensitivity of pertussis-inoculated mice to subsequent injections of pertussis may be an example of sensitivity to an endotoxin-like material rather than an example of an antigen-antibody reaction. B. S.

Histamine Sensitivity of Adrenalectomized and Pertussis-Treated Mice. Gauthier, G. F., Loew, E. R., and Jenkins, H. J.: Proc. Soc. Exper. Biol. & Med. **90**: 726, 1955.

The mechanism responsible for the pronounced increase (25 to 100 times) in histamine sensitivity in mice which is produced by injections of *Hemophilus pertussis* vaccine remains unknown. Since adrenalectomized mice are also sensitive to histamine but may receive some measure of protection by treatment with epinephrine and cortisone, it has been suggested that the reduction in adrenal cortex and medulla activity may be responsible for both phenomena. The authors, in the experiments described in this communication, found that, in the strain of mice they employed, pertussis treatment increased the sensitivity to intravenously injected histamine by 33 times. In the adrenalectomized mice of the same strain, however, no increase in susceptibility to *intravenous* histamine could be demonstrated but, following *intraperitoneal* injections of histamine in such mice, there was a three- to sevenfold increase in histamine sensitivity. The evidence clearly indicated a difference in the mechanisms involved in histamine susceptibility resulting from pertussis vaccine treatment and from adrenalectomy. B. S.

The Role of Histamine in Cutaneous Antigen-Antibody Reactions in the Rat. Brocklehurst, W. E., Humphrey, J. H., and Perry, W. L. M.: J. Physiol. **129**: 205, 1955.

The role of histamine in producing immunologic reactions in the cutis of the rabbit and guinea pig were studied intensively. A pneumococcus antigen-antibody system and an ovalbumin antigen-antibody system were employed to produce the immunologic responses. Arthus reactions were produced by the reversed passive method which consisted of injecting graded doses of antibody intracutaneously followed immediately by an excess of antigen intravenously. The animals were killed 4 hours later and the reactions were

carefully studied. The antigen used was usually a 5-times recrystallized ovalbumin. The antibody was rabbit serum which contained the specific ovalbumin antibody. Passive cutaneous anaphylaxis (P.C.A.) was also produced by the reversed technique. Graded doses of the antibody were injected intracutaneously on the abdomen of the rat, followed in 3.5 hours by an excess of antigen intravenously. The animals were killed 25 minutes after the antigen injection and mean diameters of the reaction were measured.

The histamine liberator used most frequently was 48/80 which was given in a series of intravenous injections to deplete the skins of histamine prior to the immunologic challenge. Pure antipneumococcus antibody gave P.C.A. responses similar to those seen with the cruder antibody.

It was not possible to deplete the rat skin of more than 90 per cent of its histamine content. A reduction of histamine was usually accompanied by the disappearance of the granules from the mast cells. The 10 per cent of skin histamine remaining after the use of 48/80 was not further reduced by antigen-antibody reactions to any considerable extent. Antihistamine compounds failed to block Arthus or P.C.A. reactions unless given in doses sufficient to produce signs of collapse in rats. There was no noticeable difference between the size of the Arthus and P.C.A. reactions observed in normal and in depleted rat skins. Antihistamines did not modify the immunologic reactions in depleted rat skin, although they blocked intracutaneously injected histamine. The authors conclude that histamine release is not the immediate consequence of antigen-antibody combination in the skin or the cause of the observed phenomena of cutaneous anaphylaxis. R. W.

Pharmacology, Physiology, and Pathology

Δ^1-Hydrocortisone: Plasma 17-Hydroxycorticosteroid Concentrations Following Oral and I.V. Administration. Ely, R. S., Done, A. K., and Kelley, V. C.: Proc. Soc. Exper. Biol. & Med. **91**: 503, 1956.

The Δ^1-steroids are synthetic derivatives of hydrocortisone and cortisone, differing from them by the insertion of a double bond in the 1-2 position of the steroid nucleus. They appear commercially as Metacortandralone, prednisolone, Delta-Cortef, Hydeltra, Meticortelone, and Sterane.

The Δ^1-steroids are from 3 to 5 times as active as their parent compounds in clinical effectiveness and in their effects on liver glycogen deposition, eosinophile response, etc. The writers sought to find the cause for this by a study of the absorption and metabolism of the compounds.

When Δ^1-hydrocortisone was administered orally, it produced plasma 17-hydroxycorticosteroid (17-OHCS) concentrations which were higher and of longer duration than those produced by free hydrocortisone. Larger doses of hydrocortisone (2½ times) produced higher plasma elevations of 17-OHCS but even these were of shorter duration than those produced by the Δ^1-steroid. Following intravenous doses of Δ^1-hydrocortisone, the 17-OHCS half-life was more prolonged than that following hydrocortisone. This indicated that the rate of absorption was not a factor but that the metabolism of the Δ^1-steroid was slower than that of the parent substance. The Δ^1-steroid is the only steroid which has been found thus far to have a longer half-life than hydrocortisone. It is postulated that the slower metabolism of the Δ^1-steroid may contribute to the better clinical results obtained with this steroid. B. S.

Effect of Splenectomy on Antibody Formation in Cortisone Treated Rats. Berglund, K.: Proc. Soc. Exper. Biol. & Med. **91**: 592, 1956.

In rats, splenectomy on the day following an intraperitoneal injection of a large dose of sheep erythrocytes resulted in a diminished hemolysin response during the first few days but, by the end of the first week, the hemolysin titers were normal. This suggested the importance of the role of the spleen in the early phase of antibody production. The daily administration of cortisone starting 4 to 10 days preoperatively produced a pronounced reduction in early antibody formation in the splenectomized animals. The cortisone effect in reducing antibody formation in the early preoperative days was decidedly greater in splenectomized than in sham operated animals. Splenectomy accentuated the antibody-reducing effect of cortisone. B. S.

Immunological Properties of a Form of Non-Precipitating Diphtheria Antitoxin Which Does Not Sensitize Human Skin. Studies of Its Relation to the Inhibition Reaction. Kuhns, W. J.: J. Immunol. **75**: 105, 1955.

Human subjects receiving a single booster dose of diphtheria toxoid develop precipitating and/or non-precipitating antitoxin. In the presence of high titers of non-precipitating antitoxin, there is a high incidence of immediate wheal and erythema reactions to skin tests with toxoid. This type of sensitivity could usually be transferred to normal skin. The authors now report on ten non-precipitating sera which lack the property of passive transfer and which were obtained from immunized individuals who manifested no immediate whealing reaction to toxoid. The antitoxins in these sera showed no tendency to remain fixed at the site of intracutaneous injection.

The non-precipitating non-sensitizing antitoxin behaves as "univalent" antibody and fixes complement poorly or not at all. It differs from the reagin antibody which is also "univalent" but has a high skin-sensitizing power. When mixed with appropriate mixtures of precipitating antitoxin and toxin, this non-precipitating antitoxin can be coprecipitated.

The precipitating and non-precipitating non-skin-sensitizing types of antitoxin migrate electrophoretically as slow moving ($\gamma 2$) globulin. The non-precipitating skin-sensitizing antitoxin migrates as a more rapidly moving (γ or β) globulin.

Only three of seven sera tested showed any evidence of an inhibiting effect on immediate reactions at sensitized sites when present in mixtures containing equivalent amounts of toxoid. The other four sera were too irritating on intracutaneous injection to permit evaluation of this property. B. S.

Effects of Prolonged Cortisone Therapy on the Statural Growth, Skeletal Maturation and Metabolic Status of Children. Blodgett, F. M., Burgin, L., Iezzoni, D., Gribetz, D., and Talbot, N. D.: New England J. Med. **254**: 636, 1956.

The 35 patients in this study were children receiving cortisone because of adrenocortical virilism, panhypopituitarism, hypoadrenocorticism, or severe allergic disorders. Changes in height and body weight and in roentgenographic pictures of the hands and wrists were used to measure statural growth and skeletal maturation. Periodic blood chemistry readings were also taken on pH and the concentrations of sodium, potassium chloride, carbon dioxide, nonprotein nitrogen, sugar, calcium, phosphorus, alkaline phosphatase,

and serum protein-bound iodine. The urinary content of 17-ketosteroids was also determined periodically. Electrocardiograms were obtained from time to time for the purpose of observing changes in the T waves. Twenty of the 35 children studied had allergic disease. These were considered to be endocrine-normal patients. The cortisone was administered orally and was divided into two or three doses per day.

It was found that cortisone tended to slow the rate of statural growth and skeletal maturation of children. As little as 4 to 20 mg. per square meter of body surface area per day had a marked growth-suppressing effect on hypopituitary patients. About 25 mg. per square meter per day was needed to reduce the rate of growth of patients with adrenocortical virilism from supranormal to average normal levels. The administration of 35 to 50 mg. per square meter per day tended to reduce their rates of growth and skeletal maturation to subnormal levels. A minimum of 45 mg. per square meter per day was required to reduce the growth rate of endocrine-normal children. With the exception of hypopituitary patients, there was a strong tendency for children receiving growth-suppressing doses of cortisone to undergo a compensatory spurt in growth when doses were reduced or eliminated. In growth-suppressing dosage this drug produced facial changes and obesity of the type seen in patients with Cushing's syndrome. It was tentatively concluded that cortisone may be administered over considerable periods to growing children without necessarily altering their potential ultimate stature. In endocrine-normal children who had not attained sexual maturity it was suggested that dosages be reduced below growth-suppressing levels from time to time so that the patient might regain ground lost during intervals of relatively heavy dosage. E. W.

In Vivo Studies on Precipitin Production by the Rabbit Spleen. Stevens, K. M., and Riley, P. A., Jr.: J. Immunol. **76**: 181, 1956.

Since it has been reported that the spleen plays a prominent role in antibody formation when an antigen is given intravenously, the authors sought to ascertain whether the intrasplenic administration of antigen would yield a better antibody response than the intravenous and intraportal routes. With 4 or 40 mg. doses of alum-precipitated bovine gamma globulin (AP-BGG), the peak precipitin responses in rabbits were as follows: intravenous > intrasplenic = intraportal. With soluble BGG the responses were: intravenous = intraportal > intrasplenic. Hence, the intrasplenic route of administration did not prove to be advantageous.

In order to rule out the possibility that rapid loss of antigen from the spleen was responsible for this finding, studies were done with iodinated human serum albumin (I^{131} HSA) which was administered to normal rabbits by all three routes. At 24 hours, more of the iodinated antigen was found in the spleen following intrasplenic administration than was found following the other routes. Furthermore, there seemed to be no close correlation between antibody levels and antigen (I^{131} HSA) concentration in the liver, spleen, lung, or kidney. An unusual finding was the pronounced tendency of alum-precipitated antigen to localize in the lungs. Fifteen minutes after intravenous injection, there was eight times as much intrapulmonary concentration with alum-precipitated antigen as with soluble antigen. Splenectomy resulted in a 60 per cent loss of antibody production in rabbits receiving intravenous doses of alum-precipitated BGG. B. S.

Miscellaneous

Novobiocin: A Limited Bacteriologic and Clinical Study of Its Use in Forty-five Patients. Nichols, R. L., and Finland, M.: Antibotic Med. **2**: 241, 1956.

The bacteriologic and clinical effects of novobiocin (Albamycin, Cathomycin), an antibiotic derived from a recently isolated strain of Streptomyces, were studied in 45 patients with staphylococcal disease and various infections of the urinary tract. Most patients received an initial dose of either 1 or 2 grams of novobiocin, followed by 500 mg. every 6 hours for a period of from 2 to 30 days.

In most patients with staphylococcal infections, treatment with novobiocin was clinically satisfactory. When poor results occurred, they were usually due to the emergence of resistant organisms. One 3-month-old infant with staphylococcal pneumonia died after 7 days of treatment. With Proteus infections, many strains were inhibited in vitro by relatively small concentrations of novobiocin, whereas other strains were quite resistant. In general, results in patients with coliform infection were equivocal. The most revealing data in the study, perhaps, related to the increased resistance to novobiocin which appeared during the course of therapy. It was considered desirable to explore the use of this antibiotic in combination with other antimicrobials. The only toxic effects noted during treatment with novobiocin were drug rashes and fever in 4 individuals. M. C.

I. Antigenicity of Oxypolygelatin and Gelatin in Man. Maurer, P. H.: J. Exper. Med. **100**: 497, 1954.

A purified derivative of gelatin, oxypolygelatin (OPG), having an average molecular weight of 27,000 with 1 per cent of the molecular weight distribution exceeding 100,000, was nonantigenic in guinea pigs. Human volunteers were skin tested with OPG and then bled. They were then injected with various doses of OPG daily for 9 days. Three weeks after the last injection, they were skin tested and bled again. Skin test reactions were not affected by gelatin immunization. With a microprecipitin technique, precipitable antibody was found in 13 of 20 preimmunization sera. Gelatin generally precipitated more antibody than did OPG in these sera. Following immunization, precipitable antibody level increased in 13 of 17 available sera. In three sera, there was no change, and in one antibody level decreased. Varying the OPG dose from 2 to 25 mg. did not affect antibody response. The properties of the precipitate are those of a specific antigen-antibody combination. The precipitates dissolved in antigen (gelatin) excess and picked up added protein when they were resuspended in antihuman gamma globulin serum. Quantitative analysis of antibody nitrogen precipitated by increasing amounts of gelatin and various derivatives of gelatin gave results falling into a typical precipitin curve with a central peak and lesser values at each extreme of the antigen additions. Gelatin preparations of higher molecular weight precipitated increased amounts of antibody from the serum. In a repeat experiment, 3 groups of 7 subjects each were immunized with different preparations. Blood taken 3 weeks after immunization showed decreased antibody in 5 of 7 subjects immunized with OPG. At 7 weeks, 4 of these 5 individuals showed increased antibody. In another group immunized with "high molecular weight" OPG, only one showed an increased antibody level, 3 showed a decrease, and 3 showed no change 3 weeks after immunization. At 7 weeks, of 5 subjects available, 2 showed increased levels, 2 showed decreased levels, and one showed

no change. The third group immunized with gelatin showed increased antibody at 3 weeks in one of 7 subjects, no change in one, and decreases in 5. At 7 weeks, 3 of the 6 remaining subjects showed antibody increases, 2 were unchanged, and one had antibody levels below preimmunization values. It is concluded that normally occurring antibodies to gelatin exist in human sera and that "immunization with gelatin can in many cases increase the antibody level." E. K.

Sarcoidosis, Pulmonary and Skin Studies Before and After ACTH and Cortisone Therapy. Salomon, A., Appel, B., Collins, S. F., Herschfus, J. A., and Segal, M. S.: Dis. Chest **29**: 277, 1956.

Five patients with sarcoidosis, in whom there were skin, pulmonary, parotid, and eye lesions, were treated with steroids. Four patients received ACTH and one received cortisone. The course of treatment lasted from 35 to 45 days. The total dosage of ACTH ranged from 1,500 to 2,000 units and the patient treated with cortisone received a total of 3,500 mg. During the entire course of treatment all patients were placed on a low-salt diet and were given potassium chloride and procaine penicillin. Two with positive tuberculin tests were given 1 gram of streptomycin twice a week. In those patients who had ocular, cutaneous, lymphatic, or parotid gland involvements, marked improvement in all these lesions occurred. Roentgenographic re-examination after treatment showed change of the pulmonary lesions in only one patient. Pulmonary and mediastinal lymph nodes showed improvement in two cases, increase in size in one, and no change in two. Although x-ray studies revealed extensive pulmonary changes in this disease, there was only slight impairment of pulmonary functions. It was found that the pulmonary pathology of sarcoidosis as measured by pulmonary function studies responded more slowly and to a lesser degree to adrenocorticosteroid therapy than did the lesions of the skin and other organs. E. W.

Announcement

Allergy Abstracts has been published since 1936 by members of the Allergy Division of The Jewish Hospital of Brooklyn. The Editorial Board is comprised of former residents and fellows of this department who contribute their services.

Allergy Abstracts selects and abstracts those articles in the literature which may be of clinical or theoretical interest to workers in the field of allergy. Each abstract represents a summary of the author's findings and views, and its inclusion in Allergy Abstracts does not imply approval of its contents by the editor.—*The Editors.*